REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity. The claims as presented are fully supported by an enabling disclosure. That the claims have been amended should not be taken as an indication that Applicants agree with any position taken by the Examiner. Rather the revisions have been made merely to advance prosecution. New claim 39 has been added and finds support, for example, in claim 1 as originally filed.

Claims 1-14 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and further in view of the comments that follow.

The claims as now presented do not include the terms "especially for", "if necessary" and "preferably", to which the Examiner objects.

As regards "intra-trans-tympanic, Applicants submit that the term is in no way indefinite. Indeed, at paragraph 56 of the subject application as published, details are provided regarding intra-trans-tympanic administration.

In view of the above, reconsideration is requested.

Claims 1-10 and 12 stand rejected under 35 USC 103 as allegedly being obvious over Ehrenberger et al in view of Petrus. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The present invention relates to a pharmaceutical formulation for trans-tympanic or intra-trans-tympanic administration that contains a quinoxalin-2-one derivative of

formula (I) and a compound that acts as a permeability accelerator or carrier. Neither the formulation nor the advantages thereof would have been obvious over the combination of teachings upon which the Examiner relies.

Ehrenberger et al discloses the use of 1-(aminoalkyl)-3-quinoxaline-2-one derivatives for the preparation of neuroprotective compositions (col. 1, l.6-9). Caroverine is a member of that class of derivatives (col. 1, l.35). Ehrenberger et al teaches the administration of pharmaceutically active agents (such as quinoxaline-2-one derivatives) orally or intravenously (col. 6, l.23-25, 42-44, 47-51) for the treatment of tinnitus (col. 6, l.13-14).

In contrast to Ehrenberger et al, and as pointed out above, the present invention relates to a pharmaceutical formulation comprising a quinoxalin-2-one derivative (of the formula specified in claim 1) in combination with an effective amount of a compound that acts as a permeability accelerator or carrier in respect of the derivative. The formulation of the invention is suitable for trans-tympanic or intra-trans-tympanic administration – neither of which are disclosed by Ehrenberger et al.

Petrus discloses a therapeutic composition useful for the prevention and relief of symptoms associated with ear disorders. This composition comprises anesthetics or analgesics in combination with zinc salts and penetration enhancers (see, for example, claim 1 of Petrus). The composition is described as being able to penetrate the tympanic membrane and affect the middle and inner ear (see, for example, claim 21). Penetration enhancers disclosed include dimethylsulfoxide (col. 4, l.7) and propylene glycol (col. 4, l.5), among others. Caroverine derivatives are not disclosed specifically

as anesthetics or analgesics. Moreover, nano-emulsions and liposomes are not disclosed.

The surprising and advantageous effects of the instantly claimed formulation include:

- its trans-tympanic or intra-trans-tympanic administerability,
- the easy administerability by the patient himself/herself (published application, paragraph 0008),
- the comparatively low dose that is necessary with trans- or intra-trans-tympanic administration (published application, paragraph 0004),
- the reduced risk of side reactions due to the low dose and the local administration (published application, paragraph 0005), and
- the successful treatment of muscular tinnitus that is not responsive to intravenous administration (published application, paragraph 0006).

The invention thus provides an improved pharmaceutical formulation for the treatment of inner ear diseases that can be self-administered by the patient and that involves a lower dose of active pharmaceutical agent and has a wider medical activity.

Ehrenberger et al does not teach, nor would it have suggested, the instantly claimed formulation having the above described advantages. Quinoxaline-2-one derivatives are not included among the anesthetics or analgesics taught by Petrus and, thus, the administraton of quinoxaline-2-one derivatives in combination with penetration enhancers is not taught, or even suggested, by Petrus.

As pointed out above, Ehrenberger et al teaches only oral and intravenous administration of quinoxaline-2-one derivatives. Reasonably successful oral and

intravenous administration indicate that medical effects of quinoxaline-2-one derivatives are based on transport mechanisms via the blood circulation system. The tympanum does not contain any blood vessels (see comments below). Consequently, successful administration of quinoxaline-2-one derivatives through the tympanum could not have been reasonably expected based on Petrus and Ehrenberger et al, taken alone or in combination. Furthermore, nothing in the combination of Petrus and Ehrenberger et al would have motivated one skilled in the art to combine quinoxaline-2-one derivatives with permeation enhancers. In addition, nothing in the combination upon which the Examiner relies would have provided basis for any reasonable expectation of success in treatment with quinoxaline-2-one derivatives via the tympanum, much less that medical effects could be achieved.

That muscular tinnitus could have been successfully treated when the drug was administered through the tympanum, while an intravenous treatment is not successful, would in no way have been suggested by the cited art.

In view of the above, withdrawal of the rejection is clearly in order and same is requested.

Claims 11, 13 and 14 stand rejected under 35 USC 103 as allegedly being obvious over Ehrenberger et al in view of Petrus and further in view of Mantelle. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The failings of Ehrenberger et al and Petrus are described above. Nothing in Mantelle cures those failings.

Mantelle discloses compositions for topical applications, for example, to an area of the skin, skin appendage, teeth or mucosa (col. 5, l.66-col. 6, l.3). Administration

through the tympanic membrane into the middle and inner ear is not disclosed. The compositions comprise solvents, such as propylene glycol (col. 7, l.4-5 of Mantelle) and dimethylsulfoxide (col. 8, l.18), among many more. Compounds that are known to assist in skin penetration are listed separately (col. 8, l.18-42). The list does not include propylene glycol or dimethylsulfoxide. Nano-emulsion and liposomes are not mentioned, particularly not as penetration enhancers. Caroverine as a pharmacologically active agent is mentioned for its antispasmodic effect only.

Although trans-dermal administration of caroverine is mentioned in Mantelle, the administration of the compound through the tympanum would not have been obvious for the reasons that follow.

There are fundamental differences between the anatomy of human skin and the tympanum. The tympanum has – in contrast to skin – no blood vessels at all. This means that a compound that is absorbed by the tympanum can not be expected to pass into the bloodstream of the human body. The differences between human skin and the eardrum (tympanum) become more apparent when their anatomy is examined. The eardrum consists of three layers: (a) the exterior epithelial layer, (b) a stable middle fiber layer, and (c) an interior mucosa-membrane layer. In contrast, the structure of the human skin consists of (a) the epidermis (epithelial tissue), (b) the dermis (corum, which consists of connective tissue and serves for the nutrition of the epidermis) comprising a blood vessel system of fine capillaries, and (c) the subcutis, which contains larger blood vessels and nerves for the upper skin.

Given the above-described significant differences between the anatomy of human skin and the eardrum, one skilled in the art would not have assumed a similar

behavior as regards the absorption of chemical compound. Furthermore, since the inner ear is separated by an airspace from the eardrum, even if a compound could penetrate the eardrum (which would not have been obvious due to the difference in anatomy between the eardrum and the human skin), it would not have been clear how the compound could finally reach the inner ear or what concentration levels would be necessary.

Trans-dermal administration of a drug cannot be compared to trans-tympanic administration. Therefore, Mantelle taken with Ehrenberger et al and Petrus would not have rendered the invention obvious. Indeed, it was surprising to individuals skilled in the art that caroverine could be administered through the eardrum.

In view of the above, reconsideration is requested.

Claims 1-14 stand rejected as allegedly representing obviousness-type double patenting over claims of USP 5,563,140 in view of Mantelle and Petrus. Claims 1-14 also stand rejected as representing obviousness-type double patenting over claims of USP 6,573,265 in view of Mantelle and Petrus. The Examiner's comments regarding the possibility of mooting these rejections by filing Terminal Disclaimers is noted and the Examiner is urged to hold these rejections in abeyance until the case is otherwise in condition for allowance.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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